Title: Interruption to antiplatelet therapy early after acute ischaemic stroke: A nested case-control study

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Summary

AIMS

Antiplatelet drugs are often discontinued early after ischaemic stroke, either because of poor compliance, complications or withdrawal of care. It is unclear whether this places patients at increased risk of recurrence. We explored the association between cardiovascular event rate and persistence with prescribed antiplatelet drugs.

METHODS

We used a matched case-control design using the Virtual International Stroke Trials Archive (VISTA). Cases were patients who had an acute coronary syndrome, recurrent stroke or transient ischaemic attack within 90 days post-stroke and were matched for age ±10 years and sex with up to four controls. Antiplatelet use was categorized as persistent (used for > 3 days and continued up to day 90), early cessation (used antiplatelet < 3 days) or stopped/interrupted users (used for > 3 days but stopped prior to day 90). These categories were compared in cases and controls using a conditional logistic regression model that adjusted for potential confounders.

RESULTS

A total of 970 patients were included, of whom 194 were cases and 776 were matched controls. At 90 days, 10 cases (5.2%) and 58 controls (7.5%) stopped/interrupted their antiplatelet. The risk of cardiovascular event was not different in stopped/interrupted users (adjusted OR 0.70, 95% CI 0.33, 1.48; *P*=0.352) and early cessations (adjusted OR 1.04, 95% CI 0.62, 1.74; *P*=0.876) when compared to persistent users.

CONCLUSION

We found no increased risk in patients who stopped and interrupted antiplatelets early after stroke but the study was limited by a small sample size and further research is needed.

Word: 247 words

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

Antiplatelet therapy is recommended for secondary prevention after ischaemic stroke.

Interrupting or stopping antiplatelet therapy increases the risk of cardiovascular events.

WHAT THIS STUDY ADDS

The study did not demonstrate a significantly increased risk with stopping or interrupting antiplatelet use early afte stroke. This may reassure clinicians that, where interruption to therapy is needed for clinical reasons, there is not a significant increase in short term risk.

Introduction

There is a risk of recurrence following acute ischaemic stroke [1]. Antiplatelet therapy is given to reduce this risk and the risk of other vascular outcomes [2, 3]. National Institute for Health and Clinical Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines recommend that antiplatelet therapy must be started early and continued indefinitely for long term secondary stroke prevention [3, 4]. In the UK guidelines favour aspirin therapy for 2-weeks followed by clopidogrel or the combination of low-dose aspirin and dipyridamole.

Persistence with antiplatelet regimens is variable after stroke. Rates of aspirin discontinuation of less than 10% to almost 50% reported [5, 6]. At one year as many as 50% of patients who were prescribed aspirin or clopidogrel either discontinued, or failed to adhere to their regimen [7-9]. This may be for several reasons including patient non-compliance, bleeding complications, financial pressures, or physician directed withdrawal due to withdrawal of care, intercurrent illness or planned procedures [10]. Interrupting or stopping

antiplatelet therapy may increase the risk of cardiovascular events in patients with a history of cardiovascular or cerebrovascular disease [11, 12]. One study found that among the 2197 cases of ischaemic stroke, 5.2% cases occurred within 60 days after antithrombotic withdrawal [10]. In this study, stroke events were clustered mostly in the first 7 days after stopping medication. Antithrombotic medication was stopped for various reasons including being stopped by physicians for procedures, patient compliance, bleeding complications and cost. In another study by García Rodríguez *et al*. [11], among 673 patients who had diagnosed with ischaemic stroke or TIA, 71.3% patients were taking aspirin on the day of event and 10% discontinued aspirin within 31-180 days before the event. On the other hand, a recent prospective observational study found that interruption of antiplatelet therapy due to surgical necessity was not associated with increased risk of cardiovascular events [13].

Data to demonstrate the impact of stopping antiplatelet therapy early after ischaemic stroke, where recurrence rate is highest are lacking. We aimed to explore the rate of antiplatelet cessation and interruption in a sample of patients with recent ischaemic stroke and assess the risk of cardiovascular events associated with cessation and interruption of antiplatelet drugs.

Methods

Study design

We used a matched case-control study design to examine association between antiplatelet exposure and risk of a cardiovascular event. We used individual matching to identify up to four controls for each case, matched by age ±10 years and sex. We followed the STROBE guidance in reporting this case-control study [14].

Data sources

We used data from the Virtual International Stroke Trials Archive (VISTA) [15]. VISTA is a collaborative registry that collates and provides access to anonymised data from completed clinical trials. VISTA data are stored at the Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK. VISTA contains patients' demographic data such as age, sex and ethnicity; smoking history and co-morbid conditions as well as details on the index stroke, and functional outcome measures. Adverse events (AE) data, laboratory measurements and prescribed medications are available from certain trials. All trials lodged in VISTA already have local institutional review board approved procedures in accordance with the Declaration of Helsinki. Thus, our analysis does not require a new study approval. Nevertheless, access to data is subject to approval by the steering committee.

Study cohort

All acute ischaemic stroke patients in the VISTA who took antiplatelet therapy and had complete information on initiation day of antiplatelet therapy were identified. Patients with concurrent use of vitamin K antagonist such as warfarin were excluded as it may influence clinical [16] and safety [17] outcomes in acute ischaemic stroke patients. Patients who had a cardiovascular event within the first two days after ischaemic stroke were excluded as the event might not be associated to antiplatelet but due to the specific pattern of ischaemic changes after acute stroke [18].

Cases were defined as patients who had at least one cardiovascular event in the first 90 days after acute ischaemic stroke. A cardiovascular event was defined as a acute coronary syndrome (ACS), recurrent ischaemic stroke or TIA. The event was identified from AE and SAE reports datasets using these key terms: (a) for ACS - unstable angina, acute coronary syndrome or myocardial infarction; (b) for recurrent ischaemic stroke - stroke, cerebral infarction or cerebrovascular accident; and (c) TIA - transient ischaemic attack. Controls were identified from the same source to minimize the potential of bias [19]. Controls were

defined as patients who had no cardiovascular event within 90 days after acute ischaemic stroke. The flowchart of patient's selection are shown in Figure 1. The sample size was determined by the number of cases available in the study cohort.

Antiplatelet drug exposure

The information on antiplatelet drugs was obtained from the current medication dataset in VISTA. Data on start and stop dates of antiplatelet drugs were available on certain trials that had monitored start and stop dates for all medications. Antiplatelet drugs were identified using the World Health Organization's Anatomical Therapeutic Chemical (ATC) classifications i.e. antiplatelet with ATC code: B01AC. The antiplatelet exposure period for each patient began after the diagnosis of acute ischaemic stroke and ended at the index date. The index date was the date of the first cardiovascular event recorded after antiplatelet exposure in cases. In controls it was the same date as the matched case [20, 21]. Exposure to antiplatelet drugs prior to the index date was classified as persistent use, early cessation, interruption, or stopped (Figure 2). Persistent use was defined as taking antiplatelet therapy up to, or within 3 days of the index date. Patients who switching to another antiplatelet therapy were considered as continuing antiplatelet treatment. Early cessation was defined as patient who took antiplatelet therapy less than three days post-stroke or prior to the index date. Interruption was defined as taking antiplatelet therapy up to, or within 3 days of the index date, but with two days or more interrupted use. Stopped was defined as stopping antiplatelet therapy at least 5 days before the index date.

Bleeding events

Bleeding events occurring during the study period were divided into two categories (intracerebral haemorrhage (ICH) and extracranial haemorrhage (ECH)). Intracerebral haemorrhage included all types of ICH except haemorrhagic transformation 1 and 2 of cerebral infarction, which were not counted. ECH was defined as all other types of bleeding

and was split into gastrointestinal (GI) and non-GI bleeding. These information were extracted from AE and SAE datasets in VISTA.

Statistical analysis

Descriptive statistics were recorded for cases and controls and according to the three types of antiplatelet exposures. The Chi-square test was used to compare baseline characteristics between cases and controls. Comparison between antiplatelet exposures group were conducted using the Kruskal-Wallis test or the chi-square test depending on the distribution and nature of the data. Categorical variables were summarised using frequencies and proportions and continuous variables as mean [standard deviation (SD)] or median [interquartile range (IQR)].

We used conditional logistic regression to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for risk of cardiovascular event associated with exposures of antiplatelet before the index date. We first conducted univariable analyses. In multivariable analysis, we first included all significant variables (first model). We then consecutively dropped the least significant variable until all included variables were significant at $P<0.05$ (final model). A $P<0.05$ was considered significant. Point estimates and 95% CI are presented for all results. We used a complete-case approach to analysis so there was no imputation of missing data. All analyses were performed using IBM SPSS Statistics version 21.0 [22].

A post-hoc power analysis to determine the power of the study and the sample size needed to detect a desired degree of statistical power was performed using PS (version 3.0 2009) to address the likelihood of type II error.

Results

Study population

Complete data were available for analysis of antiplatelet exposure in 4050 patients. Of thses, a total of 194 patients who had at least one cardiovascular event (126 ischaemic stroke, 45 ACS and 23 TIA) within 90 days following acute ischaemic stroke. These cases were matched to 776 controls. Baseline characteristics of patients with cardiovascular event and their matched controls are shown in Table 1. Compared with the control group, the cases were more likely to have a history of diabetes, heart failure and previous TIA. Among cases, there were 136 (70.1%) persistent users, 48 (24.7%) with early cessation and 10 (5.2%) stopped/interrupted users. Among controls, there were 534 (68.8%) persistent users, 184 (23.7%) early cessation and 58 (7.5%) stopped/interrupted users.

Patients who interrupted/stopped their antiplatelet therapy had higher baseline NIHSS and were more likely to have previous ischaemic heart disease and stroke (Table 2) than persistent users. Aspirin was the most common antiplatelet prescribed followed by clopidogrel for both cases and controls (Table 3). More than two-third of persistent users, early cessation and interrupted/stopped users were exposed to aspirin and followed by clopidogrel (Table 4). The occurrence of bleeding events was highest in interrupted/stopped users (10.3%) followed by early cessation users (7.6%) (Table 5).

Antiplatelet exposure and cardiovascular event

There was no significant difference in cardiovascular event rate in early cessation and interrupted/stopped users compared to persistent users on univariable analysis (OR 1.07, 95% CI 0.67, 1.71; *P*=0.784 and OR 0.67, 95% CI 0.34, 1.36; *P*=0.269 respectively) (Table 6). Results were similar following adjustment (adjusted OR 1.04, 95% CI 0.62, 1.74; *P*=0.876 and OR 0.70; 95% CI 0.33, 1.48; *P*=0.352 respectively) (Table 7).

Discussion

We performed a nested case-control study to explore the relationship between stopping or interrupting antiplatelet drugs and cardiovascular risk in patients with recent ischaemic stroke. We found no evidence for an increased risk of cardiovascular among patients who stopped or had interrupted use of antiplatelets.

We found that the rates of early cessation of antiplatelet therapy were higher in our study compared to others [23, 24]. We defined early cessation as taking an antiplatelet for fewer than 3 days post-stroke or before a cardiovascular event. We used this definition because most patients took aspirin and fewer than 3 days of aspirin use is unlikely to lead to full inhibition of platelets [25].

Withdrawal of antiplatelets is associated with an increase in thromboxane A2 activity [26] which could increase the risk of ischaemic stroke [10, 11, 27]. These studies found that discontinuation of antiplatelet therapy within one to six months is associated with increased risk of ischaemic stroke or TIA. We did not see an increase and several factors could explain the difference between our findings and previous studies. First, our sample size was small compared to the studies by García Rodríguez, *et al*. [11] and Broderick, *et al*. [10] so there is a risk of type 2 error. Further, previous studies have assessed different time periods and clinical scenarios. The study cohort in García Rodríguez *et al*. was followed up for approximately 3.4 years. The STRATAGEM trial assessed the interruption of antiplatelets in patients undergoing surgery [28] and found no increased risk. This suggests the risk of stopping or interrupting antiplatelet drugs may be acceptable in the short term and we wished to assess whether this was the case after stroke.

After stroke, there are several reasons why clinicians may be faced with decisions regarding continuing or stopping anti-platelets. These include bleeding complications and other adverse events such as worsening stroke symptoms or changes in haematological

measures. At present, little data exist to inform these decisions in terms of risk of recurrence following cessation. Our study should reassure that, if clinically indicated, the short term risk of stopping anti-platelets does not appear to be significantly increased.

In the present study, comorbidity was more common in cases and stroke severity was higher in patients who were interrupted or stopped users. We also found stroke severity, age, hypertension, diabetes and quality of life were related to the pattern of anti-platelet use. Patients with higher stroke severity, previous stroke and lower life quality were more likely to stop. Although we cannot be sure, this likely reflects the underlying reasons for stopping treatment, such as change in clinical condition or withdrawal of care. Early cessation users had a higher rate of atrial fibrillation which may be explained by decisions to start anticoagulation therapy. On the other hand, interrupted/stopped users had a higher rate of bleeding suggesting this also influenced the reason to interrupt or stop antiplatelet therapy.

Strengths and limitations

Despite their known problems of bias and confounding, case-control designs are efficient in examining the association between outcomes and exposures. VISTA database sample provided data that were prospectively collected during clinical trials in patients with confirmed ischaemic stroke. We minimized selection bias by including all cases of cardiovascular event within the selected time period (day 3 up to 90 days) and matched controls, free of the outcome of interest and independent of the exposure of interest. Matching for age and sex increased the precision of our results compared with those of previous unmatched case-control studies. Information on exposures was recorded in the database, eliminating recall bias.

An important limitation of this study is the lack of information on the underlying reasons for interruption/stopping of antiplatelets. This limits the generalizability of our findings to clinical

practice. Generalizability is further limited by the fact that data come from a clinical trial registry and because most patients took aspirin and few received the combination of aspirin-dipyridamole or clopidogrel as recommended in national and international guidelines. The main limitation is study power. Althought there is a large number of cases and controls, the number of patients with the different antiplatelet exposures was limited. Post hoc analysis revealed that this study, at alpha <0.05, with 194 cases and matched with four controls has insufficient power (0.239). Thus, to obtain 80% power, with the level of alpha 0.05, 801 cases with 4 matched controls per case are needed.

Conclusion

We found no significant association between interrupted or stopped use of antiplatelets and risk of cardiovascular events. This might reassure clinicians who need to stop antiplatelets for clinical reasons. However, our study had limited power and a clinically important risk cannot be excluded. Further research is needed.

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Appendix

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Competing interests

None to disclose.

Author contributions

Study concept: Ms Mazlan-Kepli, Dr Dawson. Data acquisition: Ms Mazlan-Kepli, Dr MacIsaac, Dr Dawson. Data interpretation: Ms Mazlan-Kepli, Dr MacIsaac, Dr Dawson. Preparation of initial draft: Ms Mazlan-Kepli. Critical revision of the manuscript: Ms Mazlan-Kepli, Dr MacIsaac, Prof Walters, Prof Bath, Dr Dawson. Study supervision: Dr Dawson.

References

1. Hankey GJ. Long-term outcome after ischaemic stroke/transient ischaemic attack. Cerebrovasc Dis 2003; 16: 14-19.
2. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D, Amer Heart Assoc Stroke C, Council Cardiovasc N, Council Clin C, Interdisciplinary Council Q. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011; 42: 227-76.
3. National Institute for Health and Clinical Excellence. Stroke: Diagnosis and initial management of acute stroke and transient ischaemic attack. In, London: National Institute for Health and Clinical Excellence, 2008: NICE publication no. 68.
4. Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention. In, Edinburgh: SIGN, 2008: SIGN publication no. 108.
5. Sud A, Kline-Rogers EM, Eagle KA, Fang JM, Armstrong DF, Rangarajan K, Otten RF, Stafkey-Mailey DR, Taylor SD, Erickson SR. Adherence to medications by patients after acute coronary syndromes. Ann Pharmacother 2005; 39: 1792-97.

6. Lago A, Tembl JI, Pareja A, Ponz A, Ferrer JM, Valles J, Santos MT, Stroke Project C. Adherence to aspirin in secondary prevention of ischemic stroke. Cerebrovasc Dis 2006; 21: 353-56.
7. Herlitz J, Toth PP, Naesdal J. Low-dose aspirin therapy for cardiovascular prevention quantification and consequences of poor compliance or discontinuation. Am J Cardiovasc Drugs 2010; 10: 125-41.
8. Serebruany V, Cherala G, Williams C, Surigin S, Booze C, Kuliczkowski W, Atar D. Association of platelet responsiveness with clopidogrel metabolism: role of compliance in the assessment of "resistance". Am Heart J 2009; 158: 925-32.
9. Hamann GF, Weimar C, Glahn J, Busse O, Diener HC. Adherence to secondary stroke prevention strategies - results from the German Stroke Data Bank. Cerebrovasc Dis 2003; 15: 282-88.
10. Broderick JP, Bonomo JB, Kissela BM, Khoury JC, Moomaw CJ, Alwell K, Woo D, Flaherty ML, Khatri P, Adeoye O, Ferioli S, Kleindorfer DO. Withdrawal of antithrombotic agents and its impact on ischemic stroke occurrence. Stroke 2011; 42: 2509-14.
11. García Rodríguez LA, Cea Soriano L, Hill C, Johansson S. Increased risk of stroke after discontinuation of acetylsalicylic acid: A UK primary care study. Neurology 2011; 76: 740-46.
12. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal - A special risk for late stent thrombosis. J Am Coll Cardiol 2005; 45: 456-59.
13. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, Berger PB, Iakovou I, Dangas G, Waksman R, Antoniucci D, Sartori S, Krucoff MW, Hermiller JB, Shawl F, Gibson CM, Chieffo A, Alu M, Moliterno DJ, Colombo A, Pocock S. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet 2013; 382: 1714-22.
14. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. Ann Intern Med 2007; 147: 573-77.
15. Ali M, Bath PMW, Curram J, Davis SM, Diener H-C, Donnan GA, Fisher M, Gregson BA, Grotta J, Hacke W, Hennerici MG, Hommel M, Kaste M, Marler JR, Sacco RL, Teal P, Wahlgren N-G, Warach S, Weir CJ, Lees KR. The Virtual International Stroke Trials Archive. Stroke 2007; 38: 1905-10.
16. Abdul-Rahim AH, Fulton RL, Frank B, Tatlisumak T, Paciaroni M, Caso V, Diener HC, Lees KR. Association of improved outcome in acute ischaemic stroke patients with atrial

366 fibrillation who receive early antithrombotic therapy: analysis from VISTA. Eur J Neurol 2014;
367 0: 1-8.
368 17. Shireman TI, Howard PA, Kresowik TF, Ellerbeck EF. Combined anticoagulant-
369 antiplatelet use and major bleeding events in elderly atrial fibrillation patients. Stroke 2004;
370 35: 2362-67.
371 18. Wasserman JK, Perry JJ, Sivilotti MLA, Sutherland J, Worster A, Émond M, Jin AY,
372 Oczkowski WJ, Sahlas DJ, Murray H, MacKey A, Verreault S, Wells GA, Dowlatshahi D,
373 Stotts G, Stiell IG, Sharma M. Computed tomography identifies patients at high risk for
374 stroke after transient ischemic attack/nondisabling stroke: Prospective, multicenter cohort
375 study. Stroke 2014; 46: 114-19.
376 19. Song JW, Chung KC. Observational studies: Cohort and case-control studies. Plast
377 Reconstr Surg 2010; 126: 2234-42.
378 20. Hubbard RB, Smith CJ, Smeeth L, Harrison TW, Tattersfield AE. Inhaled
379 corticosteroids and hip fracture: a population-based case-control study. Am J Respir Crit
380 Care Med 2002; 166: 1563-66.
381 21. Garbe E, Suissa S. Pharmacoepidemiology. In: Handbook of epidemiology, 2nd
382 Edition, edsAhrens W, Pigeot I, New York: Springer Science+Business Media, 2014: 1875-
383 925.
384 22. IBM Corp. IBM SPSS Statistics for Windows. In, Version 21.0 Edition, Armonk, NY:
385 IBM Corp, 2012.
386 23. Bushnell CD, Zimmer LO, Pan WQ, Olson DM, Zhao X, Meteleva T, Schwamm L,
387 Ovbiagele B, Williams L, LaBresh KA, Peterson ED, Adherence Evaluation Ischemic S.
388 Persistence with stroke prevention medications 3 months after hospitalization. Arch Neurol
389 2010; 67: 1456-63.
390 24. Bushnell CD, Olson DM, Zhao X, Pan W, Zimmer LO, Goldstein LB, Alberts MJ,
391 Fagan SC, Fonarow GC, Johnston SC, Kidwell C, LaBresh KA, Ovbiagele B, Schwamm L,
392 Peterson ED. Secondary preventive medication persistence and adherence 1 year after
393 stroke. Neurology 2011; 77: 1182-90.
394 25. Buerke M, Pittroff W, Meyer J, Darius H. Aspirin therapy: optimized platelet inhibition
395 with different loading and maintenance doses. Am Heart J 1995; 130: 465-72.
396 26. Diehl P, Halscheid C, Olivier C, Helbing T, Bode C, Moser M. Discontinuation of long
397 term clopidogrel therapy induces platelet rebound hyperaggregability between 2 and 6
398 weeks post cessation. Clin Res Cardiol 2011; 100: 765-71.
399 27. Maulaz AB, Bezerra DC, Michel P, Bogousslavsky J. Effect of discontinuing aspirin
400 therapy on the risk of brain ischemic stroke. Arch Neurol 2005; 62: 1217-20.

28. Mantz J, Samama CM, Tubach F, Devereaux PJ, Collet JP, Albaladejo P, Cholley B, Nizard R, Barre J, Piriou V, Poirier N, Mignon A, Schlumberger S, Longrois D, Aubrun F, Farese ME, Ravaud P, Steg PG. Impact of preoperative maintenance or interruption of aspirin on thrombotic and bleeding events after elective non-cardiac surgery: the multicentre, randomized, blinded, placebo-controlled, STRATAGEM trial. Br J Anaesth 2011; 107: 899-910.

29. C S, JL S, HE B, E F, AJ P, SP A. The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 2016; 44: D1054-D68.

30. Alexander S, Davenport AP, Kelly E, Marrion N, Peters J, Benson H. The Concise Guide to PHARMACOLOGY 2015/16: G protein-coupled receptors. Br J Clin Pharmacol 2015; 172: 5744-869.

31. Alexander S, Kelly E, Marrion N, Peters J, Benson H, Faccenda E. The Concise Guide to PHARMACOLOGY 2015/16: Enzymes. Br J Clin Pharmacol 2015: 6024-109.

32. Alexander S, Peters J, Kelly E, Marrion N, Benson H, Faccenda E, Pawson A, Sharman J, Southan C, Davies J, and CGTP Collaborators. The Concise Guide to PHARMACOLOGY 2015/16: Ligand-gated ion channels. Br J Clin Pharmacol 2015; 172: 5870-903.

33. Alexander S, Kelly E, Marrion N, Peters J, Benson H, Faccenda E. The Concise Guide to PHARMACOLOGY 2015/16: Transporters. Br J Clin Pharmacol 2015; 172: 6110-202.

34. Alexander S, Kelly E, Marrion N, Peters J, Benson H, Faccenda E. The Concise Guide to PHARMACOLOGY 2015/16: Overview. Br J Pharmacol 2015; 172: 5729-43.

425 Figures

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427 Figure 1. Flowchart of patients' selection.

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429 Figure 2. Determination of persistent user (a), early cessation user (b), interrupted user (c)

430 and stopped user (d) of antiplatelet exposure. AP, antiplatelet; CV, cardiovascular event.

Table 1. Characteristics of patients with cardiovascular event and their matched controls

Characteristics	No. (%)			p-value
	Overall *n=970*	Cases *n=194*	Controls *n=776*	
Age, years*	70.9(10.8)	70.9(11.3)	70.9(10.7)	NA‡
Male sex	510(52.6)	102(52.6)	408(52.6)	NA‡
Caucasian	808/934(86.5)	161/187(86.1)	647/747(86.6)	0.905
Current Smoker	267/936(28.5)	60/187(32.1)	207/749(27.6)	0.240
Baseline NIHSS†	12(8-17)	11.5(8-17)	12(8-17)	0.886
Medical history				
Hypertension	692/947(73.1)	147/194(75.8)	545/753(72.4)	0.365
Diabetes	228/970(23.5)	61/194(31.4)	167/776(21.5)	0.004
Atrial fibrillation	159/947(16.8)	37/194(19.1)	122/753(16.2)	0.389
Heart failure	65/859(7.6)	20/184(10.9)	45/675(6.7)	0.060
Ischaemic heart disease	243/915(26.6)	57/187(30.5)	186/728(25.5)	0.194
Previous TIA	69/901(7.7)	19/176(10.8)	50/725(6.9)	0.084
Previous stroke	177/886(20.0)	40/186(21.5)	137/700(19.6)	0.606
rt-PA	318(32.8)	70(36.1)	248(32.0)	0.305
Antiplatelet exposures				
Early cessation	232(23.9)	48(24.7)	184(23.7)	0.520
Stopped/Interrupted	68(7.0)	10(5.2)	58(7.5)	
Persistent	670(69.1)	136(70.1)	534(68.8)	

*Values are reported as mean (SD); †median (IQR); ‡Variables that were matched and hence not applicable. CI, confidence interval; IQR, interquartile range; NIHSS, National Institute Health Stroke Scale; TIA, transient ischaemic attack; rt-PA, recombinant tissue plasminogen activator; SD, standard deviation.

436 Table 2. Distribution of risk factors for cardiovascular event by antiplatelet exposure

Characteristics	No. (%)			p-value
	Persistent user *n=670*	Early cessation user *n=232*	Interrupted/ Stopped user *n=68*	
Age, years*	70.2(10.9)	73.6(10.0)	69.1(11.3)	
Male sex	351(52.4)	122(52.6)	37(54.4)	0.951
Ethnicity, Caucasian	556/646 (86.1)	197/222 (88.7)	55/66 (83.3)	0.444
Current Smoker	185/643 (28.8)	57/226 (25.2)	25/67 (37.3)	0.152
Baseline NIHSS†	11(8-16)	13(9-17)	17(12-20)	<0.001
Medical history				
Hypertension	473/654 (72.3)	169/225 (75.1)	50/68 (73.5)	0.716
Diabetes	164/670 (24.5)	51/232 (22.0)	13/68 (19.1)	0.502
Atrial fibrillation	91/654 (13.9)	56/225 (24.9)	12/68 (17.6)	0.001
Heart failure	38/601 (6.3)	21/196 (10.7)	6/62 (9.7)	0.105
Ischaemic heart disease	146/628 (23.2)	74/220 (33.6)	23/67 (34.3)	0.004
Previous TIA	48/623 (7.7)	16/212 (7.5)	5/66 (7.6)	0.997
Previous stroke	111/617 (18.0)	48/207 (23.2)	18/62 (29.0)	0.049
rt-PA	224(33.4)	74(31.9)	20(29.4)	0.755

437 *Values are reported as mean (SD); †median (IQR). CI, confidence interval; IQR,

438 interquartile range; NIHSS, National Institute Health Stroke Scale; TIA, transient ischaemic

439 attack; rt-PA, recombinant tissue plasminogen activator; SD, standard deviation.

440

441 Table 3. Characteristics of antiplatelet regimen prescribed

Antiplatelet regimen	No. (%)		Unadjusted OR (95% CI)	p-value
	Cases *n=194*	Controls *n=776*		
Aspirin	139(71.6)	566(72.9)	1.00	-
Clopidogrel	28(14.4)	105(13.5)	1.10 (0.69-1.74)	0.674
Aspirin+Clopidogrel	10(5.2)	25(3.2)	1.63 (0.75-3.52)	0.215
Aspirin+Dipyridamole	10(5.2)	50(6.4)	0.82 (0.40-1.68)	0.585
Ticlopidine	4(2.1)	16(2.1)	1.01 (0.34-3.05)	0.980
Aspirin+Ticlopidine	1(0.5)	1(0.1)	4.44 (0.28-71.29)	0.293
Carbasalate	1(0.5)	5(0.6)	0.76 (0.09-6.73)	0.825
Dipyridamole	1(0.5)	5(0.6)	0.79 (0.09-6.73)	0.825
Ozagrel	0(0.0)	1(0.1)	-	-
Triflusal	0(0.0)	2(0.3)	-	-

442 CI, confidence interval; OR, odds ratio.

443

444 Table 4. Frequency of antiplatelet regimen according to types of antiplatelet exposure

Antiplatelet regimen	No. (%)			p-value*
	Persistent user *n=670*	Early cessation user *n=232*	Interrupted/ Stopped user *n=68*	
Aspirin	492(73.4)	160(69.0)	53(77.9)	-
Clopidogrel	88(13.1)	38(16.4)	7(10.3)	0.267
Aspirin+Clopidogrel	20(3.0)	12(5.2)	3(4.4)	0.238
Aspirin+Dipyridamole	43(6.4)	13(5.6)	4(5.9)	0.948
Ticlopidine	13(1.9)	7(3.0)	0(0.0)	0.291
Aspirin+Ticlopidine	2(0.3)	0(0.0)	0(0.0)	1.000
Carbasalate	6(0.9)	0(0.0)	0(0.0)	0.467
Dipyridamole	4(0.6)	2(0.9)	0(0.0)	0.774
Ozagrel	0(0.0)	0(0.0)	1(1.5)	0.076
Triflusal	2(0.3)	0(0.0)	0(0.0)	1.000

445 *Compared with aspirin.

446 Table 5. Frequency of bleeding events following antiplatelet exposure

Bleeding	No. (%)			
	Persistent user *n=670*	Early cessation user *n=232*	Interrupted/ Stopped user *n=68*	Overall *n=970*
ICH	7(1.1)	6(2.7)	5(7.5)	18(1.9)
ECH	21(3.2)	12(5.4)	2(2.9)	35(3.7)
Total bleeding	28(4.2)	18(7.6)	7(10.3)	53(5.5)

447 ICH, intracranial haemorrhage; ECH, extracranial haemorrhage.

448 Table 6. Univariate analyses (conditional logistic regression) of selected variables against

449 outcome of being “case”

Characteristics	No. (%)		Unadjusted OR (95% CI)	p-value
	Cases *n=194*	Controls *n=776*		
Ethnicity				
Caucasian	161/187 (86.1)	647/747 (86.6)	0.94 (0.58-1.51)	0.782
Others	26/187 (13.9)	100/747 (13.4)	1.00	
Smoking history				
Current Smoker	60/187 (32.1)	207/749 (27.6)	1.25 (0.87-1.79)	0.219
Non/Former Smoker	127/187 (67.9)	542/749 (72.4)	1.00	
Baseline NIHSS*	11.5 (8-17)	12 (8-17)	0.99 (0.97-1.02)	0.886
Medical history				
Hypertension				
Yes	147/194 (75.8)	545/753 (72.4)	1.19 (0.82-1.72)	0.356
No	47/194 (24.2)	208/753 (27.6)	1.00	
Diabetes				
Yes	61/194 (31.4)	167/776 (21.5)	1.71 (1.20-2.46)	0.003
No	133/194 (68.6)	609/776 (78.5)	1.00	
Atrial fibrillation				
Yes	37/194 (19.1)	122/753 (16.2)	1.27 (0.82-1.95)	0.285
No	157/194 (80.9)	631/753 (83.8)	1.00	
Heart failure				
Yes	20/184 (10.9)	45/675 (6.7)	1.80 (1.01-3.20)	0.046
No	164/184 (89.1)	630 (93.3)	1.00	
IHD				
Yes	57/187 (30.5)	186/728 (25.5)	1.26 (0.89-1.80)	0.208
No	130/187 (69.5)	542/728 (74.5)	1.00	
Previous TIA				
Yes	19/176 (10.8)	50/725 (6.9)	1.78 (1.01-3.15)	0.049
No	157/176 (89.2)	675/725 (93.1)	1.00	
Previous stroke				
Yes	40/186 (21.5)	137/700 (19.6)	1.08 (0.72-1.62)	0.700
No	146/186 (78.5)	563/700 (80.4)	1.00	
rt-PA				
Yes	70 (36.1)	248 (32.0)	1.20 (0.87-1.66)	0.267
No	124 (63.9)	528 (68.0)	1.00	
Antiplatelet exposures				
Early cessation	48 (24.7)	184 (23.7)	1.07 (0.67-1.71)	0.784
Stopped/Interrupted	10 (5.2)	58 (7.5)	0.67 (0.34-1.36)	0.269
Persistent	136 (70.1)	534 (68.8)	1.00	

450 All values are reported as no. (%) unless otherwise noted. †Values are reported as median

451 (IQR). CI, confidence interval; IHD, ischaemic heart disease; IQR, interquartile range;

452 NIHSS, National Institute Health Stroke Scale; OR, odds ratio; TIA, transient ischaemic

453 attack; rt-PA, recombinant tissue plasminogen activator.

454 Table 7. Multivariable conditional logistic regression of explanatory variables against

455 outcome of being “case”

Characteristics	Adjusted OR (95% CI)	p-value*
First model, all variables		
Caucasian	0.89 (0.52-1.54)	0.684
Current Smoker	1.18 (0.77-1.81)	0.442
Baseline NIHSS	0.98 (0.95-1.02)	0.331
Hypertension	1.04 (0.65-1.67)	0.862
Diabetes	1.60 (1.03-2.49)	0.036
Atrial fibrillation	1.32 (0.76-2.29)	0.318
Heart failure	1.33 (0.69-2.55)	0.398
Ischemic heart disease	0.99 (0.65-1.50)	0.964
Previous TIA	2.15 (1.15-4.01)	0.016
Previous stroke	0.97 (0.59-1.59)	0.896
rt-PA	1.05 (0.72-1.54)	0.787
Early cessation†	1.09 (0.60-1.96)	0.779
Stopped/Interrupted†	0.72 (0.32-1.65)	0.441
Final model		
Diabetes	1.72 (1.170-2.52)	0.006
Previous TIA	1.90 (1.06-3.40)	0.031
Early cessation AP†	1.04 (0.62-1.74)	0.876
Stopped/Interrupted AP†	0.70 (0.33-1.480)	0.352

456 *Adjusted for other variables in model. †Compared to Persistent users. AP, antiplatelet; CI,

457 confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; rt-PA,

458 recombinant tissue plasminogen activator; TIA, transient ischaemic attack.

459 Tables of Links

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TARGETS	462
G protein-coupled receptors [30]	463
$P2Y_1$ receptor	$P2Y_{12}$ receptor
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470 These Tables of Links list key protein targets and ligands in this article that are hyperlinked*
471 to corresponding entries in http://www.guidetopharmacology.org, the common portal for data
472 from the IUPHAR/BPS Guide to PHARMACOLOGY [29], and are permanently archived in
473 the Concise Guide to PHARMACOLOGY 2015/16 [30-34].